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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,531	03/30/2005	Paul Dent	ON/4-32419A	8871

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ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
01/06/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,531	DENT ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on October 10, 2009.

Status of Claims

Claims 17-22 are currently pending and are the subject of this office action.

Claims 17-22 are presently under examination.

Priority

The present application is a 371 of PCT/IB03/01418 filed on 04/04/2003, and claims priority to provisional application No. 60/371,330 filed on 04/10/2002.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (Maintained Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-22 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

The reasons for this rejection have been provided in the previous office action dated July 22, 2008, the text of which is incorporated by reference herein.

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that:

"In supporting the rejection, the Examiner states that flavopiridol (FP) is the only CDK inhibitor tested. The Examiner also cites the structural diversity of CDK inhibitors as a basis to contend that different CDK inhibitors would behave differently against different biological targets. However, as recognized by the Examiner, and regardless of their structural diversity, they have a common biological property which the present specification teaches in the basis for their usefulness in the present method: CDK inhibition. Applicant asserts that is reasonable to expect other compounds with a similar biological activity to provide results similar to FP due to their common CDK inhibitor property."

Examiner's response

According to MPEP 2164.02: "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation."

In this case, Applicant provided proof of efficacy just for one CDK inhibitor (FP). Neither the prior art nor Applicant teaches any other CDK inhibitor to be effective against Bcr/Abl positive leukemia resistant to Imatinib. Since CDK inhibitors have such different structural features, and since the binding pockets of the kinases being inhibited (Bcr/Abl tyrosine kinases) are so tight, there are enough reasons to believe that, unless the other CDK inhibitors share the same structural motif as FP that are critical for binding to the Bcr/Abl tyrosine kinases, that most of the CDK inhibitors will not show the same efficacy if any as FP. In other words, there is no correlation between the CDK inhibition of a particular compound and its efficacy against Bcr/Abl positive leukemia resistant to Imatinib. Due to the uncertainty in treating Bcr/Abl positive leukemia resistant to Imatinib with CDK inhibitors in general, Applicant did not provide a representative set in order to enable for the entire genus of CDK inhibitors.

Applicant further argues:

"The Examiner also states that there is no evidence that the mixture will be synergistic at any other concentration that the one disclosed in the specification. However, evidence of synergy is not necessary to enable one to treat patients with a combination of the present invention. The case cited by the Examiner relates to an obviousness rejection, not the enablement requirement.

Examiner's response:

According to MPEP 2164.08: "All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. >See, e.g., *AK Steel Corp. v. Sollac,* 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003)(When a range is claimed, there must be reasonable enablement of the scope of the range. Here, the claims at issue encompassed amounts of silicon as high as 10% by weight, however the specification included statements clearly and strongly warning that a silicon content above 0.5% by weight in an aluminum coating causes coating problems. Such statements indicate that higher amounts will not work in the claimed invention.)."

In the instant case, Applicant claims a synergistic effect for the mixture of FP and Imatinib over a range (see claims 21 and 22) that is much broader than what is disclosed in the specification (1:7 FP: Imatinib). So, even though synergy is not required for enablement in general, it is required when "synergy" is claimed, like in the instant case. The case cited: *In re Kollman*, although normally used in prior art

rejections, it is applicable here because it shows that the claims are not commensurate in scope with the showing of synergy, except for the narrow range disclosed in the specification (see above).

Finally, Applicant argues:

"The Examiner further states that the specification is silent about the correlation between the preclinical experiments (i.e. *in vitro* data) and *in vivo* success."

"The Examiner cites Shah et. al. to support the position that animal data is required to make a reasonable prediction about a drug that is effective in vitro for the treatment of Bcr/Abl Imatinib resistant cells. Although this reference discloses both cell line and animal experiments with BMS-354825, it does not support the position that the animal experiments were required before one would reasonably conclude that BMS-354825 would have utility for CML. Applicant requests the Examiner to point out the particular portions of this publication that are relied on. Applicant further asserts that experiments in cell lines are predictive."

Examiner's response:

Shah teaches that there are 15 Bcr/Abl mutants and that BMS-354825 inhibited 14 of those 15, except for the Thr315Ile mutation (see abstract and page 91, left column, first paragraph). Also O'Hare (Expert Opinion on Investigational Drugs (2008) 17:865-878, cited for evidentiary purposes and not as part of the rejection itself) teaches that: "Despite the excellent results in patients with Imatinib-resistant or Imatinib-intolerant CML treated with nilotinib or desatinib, early indications suggest that: the

cross resistant Bcr/Abl Thr315Ile mutant is disproportionately represented among patients who relapse on these therapies; each Abl inhibitor exhibits vulnerabilities to certain kinase domain mutations" (see abstract). Applicant, on the other hand, did not provide any evidence against which mutants FP is effective. So the *in vitro data* provided by Applicant, does not correlate with the efficacy *in vivo*, since other mutations, against which FP is not effective and that were not present *in vitro*, will be present in animals or humans.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
December 30, 2009

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612